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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,500	04/11/2001	Glenn Richard Carlson	98-039B	2455
7590	05/12/2005		EXAMINER	
			SULLIVAN, DANIEL M	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 05/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/832,500	CARLSON ET AL.	
<b>Examiner</b>	<b>Art Unit</b>	Daniel M. Sullivan	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) Responsive to communication(s) filed on 09 December 2004 and 07 March 2005.  
 2a) This action is **FINAL**.                            2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) Claim(s) 3-5,7-9,11-13,15-17,19 and 20 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 3-5,7-9,11-13,15-17,19 and 20 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|  | 6) <input type="checkbox"/> Other: _____                                    |



## **DETAILED ACTION**

This Office Action is a reply to the Papers filed 9 December 2004 and 7 March 2005 in response to the Non-Final Office Action mailed 9 September 2004. Claims 1-17, 19 and 20 were considered in the 9 September Office Action. Claims 1, 2, 6, 10 and 14 were canceled in the 7 March Paper. Claims 3-5, 7-9, 11-13, 15-17, 19 and 20 are pending and under consideration.

### ***Response to Amendment and Arguments***

Rejection of claims 1, 2, 6, 10 and 14 is rendered moot by the cancellation thereof.

### **Claim Rejections - 35 USC § 112**

Claims 3-5, 7-9, 11-13, 15-17, 19 and 20 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to modulate gene expression *in vitro* or in a plant, does not reasonably provide enablement for the method practiced in animals *in vivo*. In the previous Office Action, it was established that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As stated in the previous Office Action, the instant disclosure fails to provide a single working example of the claimed method practiced in an animal *in vivo*. Although, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

*In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970), lack of a working example is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. As the teachings cited in the Office Action clearly establish the gene therapy art as unpredictable, the specification must disclose the claimed method in such a manner that one

skilled in the art would be able to practice the method for its intended purpose (*i.e.*, gene therapy) without having to engage in undue experimentation. However, the guidance in the specification with regard to practicing the method in an animal *in vivo* is limited to lists of potentially therapeutic nucleic acid constructs (*e.g.*, page 13) and generic statements such as, “[s]uitable routes of administering the pharmaceutical preparations include oral, rectal, topical...[etc.].” The specification provides no specific guidance to address the myriad of problems encountered in developing therapeutically viable methods involving exogenous gene expression.

The Office Action concludes that, although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would not be able to use the methods *in vivo* for the purpose contemplated in the specification without first engaging in undue experimentation. While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels (*i.e.*, levels providing no patentably useful phenotypic effect), the skilled artisan would have to engage in trial and error experimentation to achieve expression of a particular molecule at levels sufficient for therapeutic effect. Given the many factors affecting gene transfer and expression *in vivo* and the absence of existing working examples the level of experimentation required is clearly beyond what is considered routine in the art. Therefore, the teachings of the specification and prior art would not enable the ordinary skilled artisan to make and use the invention without undue experimentation.

In response, Applicant contends that it is understood in the art that the use of a method to modulate gene expression in multicellular organisms does not apply only to gene therapy. Applicant asserts that the claimed method might also be used in transgenic animals and non-transgenic animals and that the specification describes the use of the present method to modulate

gene expression in transgenic organisms. Applicant cites a teaching at page 1, lines 17-19, which states that inducible expression according to the method of the instant claims can be valuable for foreign protein production, for example, therapeutic proteins, industrial enzymes, polymers and the like. Applicant concludes that the Examples of *in vitro* mammalian gene expression, the teachings in the specification on how to use the gene expression method and the high level of knowledge and skill in the art provide sufficient disclosure of the manner in which the invention can be made and used.

These arguments have been fully considered but are not deemed persuasive. Even if one accepts that the process claimed has uses other than gene therapy, Applicant is reminded that the enabled scope must bear reasonable resemblance to the scope of protection sought. “Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without “undue experimentation.” *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404; *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification).” *In re Wright* (CAFC) 27 USPQ2d 1510 at 1513.

As described in the previous Office Action, page 5, the specification clearly teaches that methods of gene therapy are within the scope of what is claimed. Therefore, enablement for the broad scope of the claimed method requires enablement for the therapeutic methods embraced thereby. Furthermore, even if the skilled artisan would have understood that the claims also encompass the method practiced in transgenic organisms, the specification fails to provide

teachings that would enable even a method limited to practice in transgenic animals. For example, the claims clearly encompass the method practiced in humans and, given that neither the application nor the art teach a manner and process of making a transgenic human, the relevant art is undeveloped and unpredictable. Still further, even if the method were limited to practice in non-human animals, the art teaches that useful production of foreign therapeutic proteins, industrial enzymes, polymers and the like in transgenic animals is also unpredictable. In reviewing the relevant literature, Houdebine (*Transgen. Res.* (2000) 9:305-320) describes a myriad of obstacles that have been encountered by artisans seeking to express recombinant proteins in mammals at pharmaceutically relevant levels. In the abstract, Houdebine identifies three major sources of unpredictability in the art. First is the unpredictability of transgene expression; second is the unpredictability of proper posttranslational modification; and third is the unpredictable effects of high-level recombinant expression on the host mammal. Houdebine, which was published at approximately the same time as the instant application was filed, teaches, "the mammary gland is presently the only really available animal bioreactor" (page 315, column 1, paragraph 7). Thus, methods for pharmaceutically relevant production or recombinant proteins in mammalian organs and tissues outside of mammary gland were unavailable to the skilled artisan. With regard to production of pharmaceutical proteins in milk, Houdebine teaches, "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" (paragraph bridging pages 309-310).

Significantly, Houdebine points out that experiments carried out *in vitro* using cultured cells are poor predictors of expression *in vivo*. In the third paragraph in the first column on page 314, Houdebine states, "[cultured mammary] cells can at best predict the intrinsic potency of a

construct for transcription but not the level of expression in transgenic animals. The cell lines are not expected to be able to reflect all the events, which mature the proteins post-transcriptionally.”

Houdebine further teaches that proper posttranslational processing of proteins expressed at pharmaceutically relevant levels is often unpredictable because the mechanisms are dependent on cellular enzymes that are present at variable concentrations in different cell types (paragraph bridging columns 1 and 2 on page 313). Importantly, because proper glycosylation is vital for pharmacological activity of many proteins, Houdebine teaches that mammary cells do not always glycosylate recombinant proteins in an appropriate manner even when the protein is naturally secreted in milk in a glycosylated form (see the example of bile salt-stimulated lipase presented in the second full paragraph in the right column on page 313). Houdebine teaches that the reasons why some proteins are not correctly glycosylated are particularly complex and might be related to the superphysiological production of the recombinant protein. Furthermore, in the paragraph bridging columns 1 and 2 on page 310, Houdebine teaches that obtaining high-level expression of proteins that are not naturally secreted is particularly problematic. When viewed as a whole, the teachings of Houdebine, which are based on a review of the art as of the filing date of the instant claims, clearly show that obtaining pharmaceutically useful expression of a protein in a mammal was only enabled for a limited set of proteins in mammary tissues, and production of pharmaceutically useful amounts of any given protein in mammary tissue was unpredictable. Given these teachings, the skilled artisan would not expect that a broad method such as the one claimed in the instant application could be used to provide useful production of therapeutic proteins, industrial enzymes, polymers and the like without undue experimentation to surmount the obstacles recognized in the art.

Thus, developing the claimed method such that it could be used even for those embodiments that Applicant asserts to be enabled would require undue experimentation. Therefore, the record as a whole clearly demonstrates that the process claimed is not enabled beyond the scope of *in vitro* or in a plant.

***Claim Rejections - 35 USC § 102***

Claims 3-5, 7-9, 11-13, 15-17 and 20 stand rejected under 35 U.S.C. 102(e) as being anticipated by Albertsen *et al.* US Patent No. 6,504,082 (effective filing date 10 September 1998).

As described in the previous Office Action, Albertsen *et al.* teaches a method to modulate exogenous gene expression comprising contacting a complex comprising a DNA binding domain, a ligand binding domain, a transactivation domain and a ligand with a DNA construct comprising the exogenous gene under the control of a response element and Albertsen *et al.* teaches that a preferred embodiment of the ligand is methoxyfenozone, which meets the structural limitations of the ligand of the instant claims.

In response to the *prima facie* case of record, Applicant argues that Albertsen *et al.* is anticipated by the priority date of the instant application. Applicant argues that the provisional application 60/089,546 discloses the method claimed in the instant application and urges, “[t]he ligands contemplated within the method claims of priority applications 60/089,546 and 09/210,010 are still explicitly described and claimed in the present divisional application. Therefore the present claims, for specifically shared teachings (method of modulating gene expression and certain species of ligands), should enjoy the benefit of the priority applications

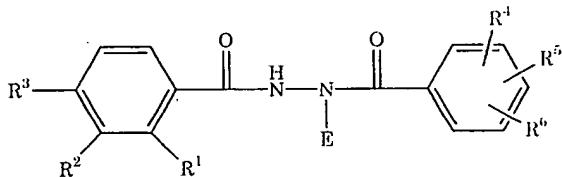
for those particular teachings” (page 13). Applicant further argues that the priority applications describe, teach and claim the use of the ligand, methoxyfenozide, as contemplated by Albertson *et al.* Applicant asserts that Albertson *et al.* only tested tebufenozide, which the instant applications teach away from and that the priority applications explicitly describe and claim the use of the preferred compound, methoxyfenozide, as well as improvements over the compound tested in Albertson *et al.* Applicant concludes, based on this, that the instant application should enjoy the benefit of the priority documents.

These arguments have been fully considered but are not deemed persuasive. As stated in the previous Office Action, “the claims of the instant application are directed to methods of using genus of ligands having limitations not explicitly or implicitly contemplated in the parent applications, [therefore] the claims do not enjoy support of the ‘010 and ‘546 applications” (page 3).

According to MPEP §2163, “[t]o comply with the written description requirement of 35 U.S.C. 112, para. 1, or to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. When an explicit limitation in a claim ‘is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation.’” (quoting *Hyatt v. Boone*, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998); emphasis added) and, “[t]he introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph.

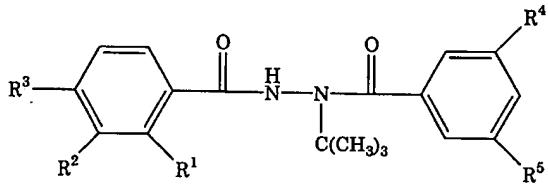
See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).".

In the instant case, the generic compound of the claims comprises the structure:



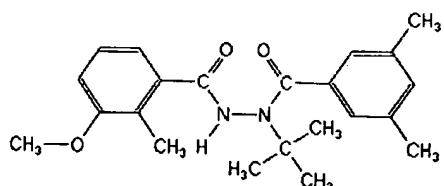
, while the priority documents disclose a

compound comprising the structure:



. The Examiner can find no support for generic "E" or "R<sup>5</sup>" of the claimed compound in the priority document disclosures. Furthermore, as stated in the previous Office Action, the R groups of the instant claims are subject to a list of provisos not contemplated in the priority documents (see, e.g., elements (a)-(i) following "provided that:" in the instant claim 1).

Applicant appears to be asserting that disclosure of the species methoxyfenozide provides support for the compound of the instant claims. However, the subgenus of compounds to which the claims are now limited was not described in the priority documents. Absent evidence to the contrary, disclosure of methoxyfenozide, which has the structure:



, does not support the subgenus of compounds now used in the claimed method. For example, neither the generic "E" nor "R<sup>5</sup>" groups of the instant claims

is found in the structure of methoxyfenozide and the Examiner can find no blaze marks directing the skilled artisan to include those elements or to limit the compound to the various provisos now recited in the claims. In order to obtain benefit of the priority documents for claims to using the compound as presently recited, Applicant must clearly indicate where support for the subgenus as defined in the instant claims can be found in the 09/210,010 and 60/089,546 applications.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 USC §102 as anticipated by Albertsen *et al.*

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.  
Examiner  
Art Unit 1636

  
DAVID GUZO  
PRIMARY EXAMINER  
